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Original Research Article

An experimental evaluation of therapeutic effect of Rosa damascena in hepatotoxicity induced by isoniazid

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ABSTRACT

Objectives: Hepatotoxicity occurs as a side effect of first line anti-tubercular drug such as Isoniazid. The aim of the present study was to evaluate therapeutic potential of ethanolic extract of Rosa damascene flowers (RDEE) in isoniazid induced hepatotoxicity in rats.**Methods:** Rats were given orally isoniazid (50 mg/kg) for 28 days. Silymarin (50 mg/kg) was administered as standard drug. From 29th to 43rd day of the study, isoniazid was stopped and therapeutic agents such as normal saline, silymarin, RDEE 1.5g/kg and 3g/kg were given orally in different animal groups respectively. On 44th day, blood samples were collected for biochemical analysis and liver tissue was subjected to histopathological examination.**Results:** The rats administered RDEE showed significant reduction in the liver marker enzymes and total bilirubin treated as compared to negative control group. There was also significant improvement in antioxidant levels and histopathological scores in RDEE treated group in comparison to the negative control group.**Conclusion:** This study demonstrates the beneficial effect of ethanolic extract of Rosa damascene flowers (RDEE) as a therapeutic agent in hepatotoxicity induced by isoniazid in a dose dependant manner.© This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1. Introduction

As per the WHO, India has the highest Tuberculosis burden, with around 23% of the global estimate of new cases.¹ Hepatotoxicity, a common adverse effect of the antitubercular drugs leads to discontinuation of therapy. Among the first line antitubercular drugs, Isoniazid and pyrazinamide have the highest reported hepatotoxicity. Their concomitant use often leads to fulminant hepatitis with lethal consequences.² Isoniazid is the leading cause of hepatotoxicity in the United States.³ Isoniazid elevates the levels of hepatic transaminases. Hepatic damage with isoniazid therapy is rare in individuals below the age of 20, but increases to 1.2% between the age of 35 to 49 years and approximately 2.3% in 50 and above age group.⁴

The hepatotoxicity of isoniazid is mostly dose related but sometimes due to drug hypersensitivity. The hepatic damage by isoniazid can be due to genetic polymorphism in acetylation. Other risk factors include old age, malnutrition, alcoholism, HIV infection and Hepatitis B or C infection.⁵

Rosa damascena Mill is a well-known flowering plant and cultivated in gardens in several places in Kashmir, Bangal and Punjab.⁶ This plant contains flavonoids such as caempferol and quercetin and their glycoside derivatives,^{7,8} carboxylic acids,⁹ terpene, myrcene, tannins and vitamin C.¹⁰ Along with its perfuming effect, flowers and petals of Rosa damascena possess medical properties. It has been used as anti-inflammatory,⁹ cardiotonic,¹¹ mild laxative,¹² cough suppressant¹⁰ and also for the treatment of menstrual bleeding and digestive problems.¹³ Recent studies demonstrated anti-HIV,⁷ anticonflict,¹⁴

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antibacterial,¹⁵ antitussive¹⁶ and respiratory smooth muscle relaxant¹⁷ properties for this plant.¹⁸ *R. damascena* protects against CCl₄ induced hepatotoxicity by its free radical scavenging activity.¹⁹ Alam MA et al demonstrated hepatoprotective and antioxidant effect of ethanolic extract of *Rosa damascena* flowers at 1.5g/kg and 3g/kg doses in paracetamol induced hepatotoxicity.⁶ But there are no studies conducted to evaluate the protective activity of *Rosa damascena* flowers against antitubercular drug induced hepatotoxicity. Therefore, it was worth to evaluate the therapeutic aspect of ethanolic extract of *Rosa damascena* flowers (RDEE) in isoniazid induced hepatotoxicity in rats.

2. Materials and Methods

2.1. Animals

Adult wistar albino rats of either sex (150-200g) were obtained from Central Animal House of the medical college. They were kept under standard conditions (temperature 27 ± 2°C, Humidity 30-70% & 12 hour light/dark cycles) and fed with standard pellet diet and water ad libitum. Prior to the experiments, the rats were acclimatized to the laboratory condition for 1 week. The ethical clearance was obtained from the Institutional Animal Ethics Committee (IAEC). The animal experiments were carried out in accordance to the rules and regulations of IAEC & CPCSEA.

2.2. Extract preparation

The flowers of *Rosa damascena* were procured from Dawakhana Tibbiya College, A.M.U., Aligarh, and identified by Prof. S. H. Afaq, Pharmacognosy Section, Department of Ilmul Advia, A.K.T.C., A.M.U., Aligarh, Uttar Pradesh, India. Shade-dried flowers were coarsely powdered and then subjected to extraction in ethanol for 72 h using Soxhlet apparatus. The extract was filtered using Whatman No. 1 filter paper, evaporated on a water bath at 50°C until it dried completely, and stored in the refrigerator for further use. The yield of RDEE was found to be 27.6%.

2.3. Induction of hepatotoxicity

Hepatotoxicity was induced in the animals by administering isoniazid 50mg/kg orally for 28 days.²⁰

3. Experimental model

The albino rats were divided into five groups of 6 animals each. All the drugs were given orally.

Isoniazid dissolved in distilled water was administered to all animals for 28 days. From 29th day isoniazid was stopped and the therapeutic and test agents were given for the next 15 days.

On 44th day, the animals were sacrificed and blood subjected to biochemical analysis (Serum Billirubin, AST, ALT and ALP). The liver was removed and physical

parameters (weight of the liver per 100 gram of rat's weight and volume of the liver in ml per 100 gram of the rat's weight) were recorded. The liver was then subjected to histo-pathological analysis.

3.1. Biochemical evaluation

The blood samples were collected by cardiac puncture (open approach) and centrifuged at 5000 rpm for 10 minutes, plasma was separated and subjected to biochemical analysis. Total bilirubin was estimated using the method described by Jendrassik L. et al. 1938²¹ using reagent supplied by Accurex Biomedicals Pvt Ltd. India. AST and ALT levels were determined by the Reitman and Frankel²² method using kits acquired from Span Diagnostics Ltd. (Surat, India). Serum ALP levels were estimated by King's method²³ using the ALP determination kit procured from Beacon Diagnostics, Gujrat India.

3.2. Antioxidant tests

The homogenate of the liver (in 10% weight/volume of phosphate buffer [0.2 M, pH-6.6]) tissue was used to perform in vivo antioxidant tests such as Catalase [CAT],²⁴ reduced glutathione [GSH],²⁵ and malondialdehyde (MDA).²⁶

3.3. Histological examination

The liver samples were processed according to standard histological techniques and stained with hematoxylin and eosin.²⁷ The assessment of damage of liver tissue was done by method described by Davidson C.S. 1979.²⁸

The percent of hepatoprotection offered by the standard and test agents was calculated using the formula:

$$H \left[1 - \left(\frac{T-V}{C-V} \right) \right] \times 100$$

Where H = Percentage of hepatoprotection, T = Mean value of group treated with test agent, C = Mean value of group treated with Isoniazid, V = Mean value for normal control group animals.

3.4. Statistical analysis

The data values are expressed as Mean ± Standard Error of Mean (SEM). The groups were compared by one-way analysis of variance (ANOVA) followed by post hoc Tukey's test to analyze the statistical significance. P < 0.05 was considered significant for this study.

4. Results

4.1. RDEE effect on liver enzymes

The markers assessed were total bilirubin, AST (aspartate aminotransferase), ALT (alanine aminotransferase) and ALP (alkaline phosphatase). In the Group II, total bilirubin (p<0.001), AST (p<0.001) and ALT (p<0.001) was raised

significantly along with ALP level ($P < 0.01$) in comparison to the Group I. All the parameters except ALP in Group III showed significant reduction, total bilirubin ($p < 0.001$), AST ($p < 0.001$) and ALT ($p < 0.001$) in comparison to the Group II. ALP in the Group III also showed reduction but were not statistically significant when compared to the Group II. In Group IV bilirubin levels showed significant ($p < 0.001$) reduction in comparison to the Group II. Serum ALT levels also exhibited significant ($p < 0.01$) reduction, serum AST and ALP levels were reduced but were not statistically significant in comparison to Group II. RDEE high dose (Group V) exhibited significant reduction in the levels of total bilirubin ($p < 0.001$), AST ($p < 0.01$) and ALT ($p < 0.001$) when compared to the Group II, the ALP levels also showed reduction in comparison to the Group II but it was not statistically significant (Table 2).

4.2. RDEE as antioxidant

There was a significant decrease in the levels and activity of GSH and CAT in INH alone treated group. RDEE showed an increase in the levels of CAT ($p < 0.001$), thereby suggesting a correction in oxidative stress. There was a significant increase in the levels of GSH ($p < 0.001$) and a decrease in MDA ($p < 0.001$) levels in RDEE treated groups as compared to negative control (Table 2).

4.3. Percentage of Hepatoprotection offered by RDEE

Percentage of hepatoprotection was highest for the Group III i.e. 80.8%, 89.6%, 82.1% and 55.1% for bilirubin AST, ALT and ALP respectively. Among the RDEE test groups hepatoprotection for the Group IV was 65.6%, 32.5%, 58.2% and 31.1% as compared to 71.3%, 67.1%, 73.1% and 41.5% for Group V.

4.4. Histopathological examination

The microscopic appearance of liver appeared to be normal in the Group I with no degeneration, necrosis and fibrosis. In Group II, the liver histopathological score was grossly deranged with significant degeneration ($p < 0.001$), necrosis ($p < 0.001$) and fibrosis ($p < 0.001$) with no regeneration in comparison to Group I. In Group III, the scores showed betterment. The degeneration ($p < 0.001$), necrosis ($p < 0.05$) and fibrosis ($p < 0.05$) scores exhibited significant reduction and also there was significant increase in regeneration ($p < 0.001$) in comparison to the Group II. In Group IV, there was a decrease in the degeneration, necrosis and fibrosis scores but were not statistically significant and also there was significant regeneration ($p < 0.01$) in comparison to the Group II. In Group V, the degeneration ($p < 0.01$), necrosis scores ($p < 0.05$) and fibrosis scores ($p < 0.05$) exhibited significant reduction and also there was significant regeneration ($p < 0.001$) in comparison to the Group II (Table 4).

5. Discussion

Despite of advances in the modern medicine era, there is no definitive cure for liver related diseases. Hence, there is an overwhelming need to develop newer agents, which not only prevent damage but also be cures hepatic disease.

Isoniazid (INH) is used for prophylaxis as well as treatment of TB. It is associated with significant hepatotoxicity. Hepatotoxicity in patients on INH treatment if not recognized timely can have fatal results³⁰. INH converts to acetylisoniazid by the enzyme NAT2 which then gets eliminated by the kidney; acetylisoniazid further gets transformed into acetylhydrazine and then to another highly hepatotoxic metabolite acetyl diazine by the CYP enzymes which is toxic by itself as it gets converted to reactive acetyl onium ion, acetyl radical and ketene, which binds covalently to hepatic macromolecules causing irreversible damage to the hepatocytes.²⁹ In our study, we administered INH in a dose of 50 mg/kg orally for 28 days to induce hepatotoxicity in rats.

Since long time herbal therapy for liver diseases has been used. Despite of commercial popularity of many herbal remedies for liver diseases, they still remain unacceptable. Therefore, to develop drugs effective in liver disease based on these knowledge, proper therapeutic evaluation of herbal products in animal models is needed.³⁰

In the present study, we explored the therapeutic benefits of RDEE in isoniazid induced hepatic damage in rats. Results of the biochemical parameters demonstrates that 15 days treatment with RDEE in both doses resulted reduction in AST, ALT and bilirubin levels significantly as compared to negative control group. All the parameters except ALP in animals of positive control group showed significant reduction, total bilirubin ($p < 0.001$), AST ($p < 0.001$) and ALT ($p < 0.001$) as compared to negative control group. ALP value in positive control group also showed reduction but was not statistically significant when compared to negative control group. In rats of RDEE 1.5g/kg group bilirubin level showed significant ($p < 0.001$) reduction as compared to negative control group. Serum ALT level also exhibited significant ($p < 0.01$) reduction, serum AST and ALP levels were reduced but were not statistically significant as compared to negative control group. Animals treated with RDEE 3g/kg exhibited significant reduction in the levels of total bilirubin ($p < 0.001$), AST ($p < 0.01$) and ALT ($p < 0.001$) when compared to negative control group, ALP level also showed reduction as compared to negative control group but it was not statistically significant. The percentage of hepatoprotection offered by RDEE was almost similar to the standard drug silymarin.

The hepatoprotective activity of RDEE shown in the parameters are supported by the findings of histopathological examination. Liver sections of animals treated with RDEE exhibited significant liver protection against INH in this study, which is evident by the presence

Table 1: Grouping of animals

| Groups | Day 1-28 | Day 29-43 |
|-----------|-----------------------|-----------------------|
| Group I | Normal saline 1ml/kg. | Normal saline 1ml/kg. |
| Group II | Isoniazid 50mg/kg. | Normal saline 1ml/kg. |
| Group III | Isoniazid 50mg/kg. | Silymarin 50mg/kg21. |
| Group IV | Isoniazid 50mg/kg. | RDEE 1.5g/kg6. |
| Group V | Isoniazid 50mg/kg. | RDEE 3g/kg6. |

Table 2: Therapeutic effect of RDEE on biochemical parameters in isoniazid induced hepatotoxicity in rats

| Groups (n= 6) | T.Bilirubin (mg/dl) | S. AST (units/l) | S. ALT (units/l) | S. ALP (units/l) | CAT (U/min/mg) | GSH (μmol/mg) | MDA (nmol/mg) |
|-------------------------------------|------------------------|---------------------|---------------------|---------------------|-------------------|------------------|------------------|
| Group I (N. saline) | 0.29± 0.42 | 44.40± 5.01 | 20.64± 5.75 | 56.40± 4.82 | 84.1±4.9 | 5.29±0.29 | 204.8±8.9 |
| Group II (INH +N. saline) | 1.86 ±0.18*** | 114.40 ±6.33*** | 115.78 ±12.14*** | 119.40 ±7.42** | 47.4±2.8*** | 2.30±0.25*** | 430.1±17.6*** |
| Group III (INH + Silymarin) | 0.59 ±0.11*** | 51.64 ±10.68*** | 37.63 ±10.14*** | 84.68 ±12.95 | 69.8±2.2*** | 4.58±0.13*** | 254.8±7.8*** |
| Group IV (INH + RDEE 1.5g/kg) | 0.83 ±0.06*** | 91.62 ± 4.26 | 60.30 ±5.96** | 99.80 ± 5.57 | 59.8±2.2*** | 4.02±0.19*** | 279.4±10.2*** |
| Group V (INH+RDEE 3g/kg) | 0.74 ±0.03*** | 67.38 ±12.78** | 46.11 ±10.15*** | 93.20± 13.36 | 65.0±1.6*** | 4.60±0.12*** | 265.4±6.3*** |

All data are expressed as Mean± SE. Negative control (Group II) group was compared with Normal control group (Group I) and all other groups (Group III, IV and V) were compared with Negative control group (Group II), * p< 0.05, **p<0.01 and ***p<0.001 were considered significant.

Table 3: Percentage of Hepatoprotection offered by RDEE in isoniazid induced hepatotoxicity in rats

| S.No. | Groups n=6 | Hepatoprotection (%) | | | |
|-------|-------------------------|----------------------|------|------|------|
| | | T.Bilirubin | AST | ALT | ALP |
| 1 | Group III (Silymarin) | 80.8 | 89.6 | 82.1 | 55.1 |
| 2 | Group IV (RDEE 1.5g/kg) | 65.6 | 32.5 | 58.2 | 31.1 |
| 3 | Group V (RDEE 3g/kg) | 71.3 | 67.1 | 73.1 | 41.5 |

Table 4: Therapeutic effect of RDEE on histopathological scores in isoniazid induced hepatotoxicity in rats

| Groups n= 6 | Degeneration | Necrosis | Fibrosis | Regeneration |
|----------------------------------|--------------|--------------|--------------|--------------|
| Group I (N.saline) | 0 | 0 | 0 | 0 |
| Group II (INH +N. saline) | 2.75±0.25*** | 2.25±0.25*** | 3.00±0.40*** | 0 |
| Group III (INH + Silymarin) | 0.50±0.29*** | 0.75±0.48* | 1.25±0.47* | 2.75±0.25*** |
| Group IV (INH + RDEE 1.5g/kg) | 1.74±0.25 | 1.26±0.24 | 2.23±0.26 | 1.74±0.26** |
| Group V (INH + RDEE 3g/kg) | 0.76±0.25** | 1.01±0.42* | 1.49±2.87* | 2.50±0.29*** |

All data are expressed as Mean± SE. Negative control (Group II) group was compared with Normal control group (Group I) and all other groups (Group III, IV and V) were compared with Negative control group (Group II), * p< 0.05, **p<0.01 and ***p<0.001 were considered significant.

of regenerating and lesser degenerating hepatocytes, fibrotic bridges and necrotic foci in the prophylactic study. The protection offered by RDEE 3g/kg dose though somewhat lesser than the standard drug silymarin but was considerable when compared to the liver slices of the rats treated with isoniazid (INH) alone.

Oxidative stress is one of the major mechanisms by which isoniazid (INH) and rifampicin cause damage to the hepatocytes. During combined treatment, glutathione and related thiols, which prevent tissue from oxidative damage, get reduced in blood and liver tissue. This results in microvesicular deposition of fats in the hepatocytes and inflammation of portal triad.³¹ The likely reason of RDEE's protection against INH induced hepatotoxicity may be due to its antioxidant activity. RDEE improved CAT, glutathione and MDA significantly. Alam M et al. had also described the antioxidant effect of RDEE in their study.⁶

6. Conclusion

RDEE administration significantly improved the liver parameters in a dose dependent fashion. These results are of a preliminary study and further detailed investigations are required to pinpoint the mechanism of hepatoprotection offered by RDEE.

7. Source of Funding

None.

8. Conflict of Interest

The authors declare that there is no conflict of interest.

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